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PROVISIONAL APPLICATION COVER SHEET

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TITLE OF THE INVENTION (280 characters max)

POLYFLUORINATED CATALYSTS

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification — Number of Pages 12 — ☐ Small Entity Statement _____

☒ Drawing(s) — Number of Sheets 1 — ☐ Other (specify)

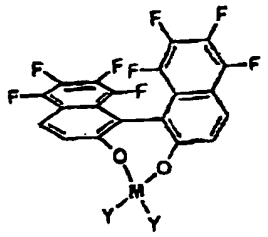

FIG. 1

Metal Catalyst using Fluorinated BINOL Based Catalyst

METHOD OF PAYMENT (check one)

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Respectfully submitted,

Signature: _____ Date: July 21, 1999

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UNITED STATES

Title: POLYFLUORINATED CATALYSTS

Inventors: Andrei Konstantin Yudin, Leo James Patrick Martyn and Subramanian Pandiaraju

FIELD OF THE INVENTION

The present invention relates to the design and method of synthesis of asymmetric catalysts and more particularly the present invention provides a new generation of polyfluorinated catalysts.

BACKGROUND OF THE INVENTION

Modern asymmetric synthesis often calls for catalytic transformations. Many important discoveries in this area are due to serendipity, however, understanding the balance of steric and electronic factors is required in order to fine-tune a catalyst toward optimal rate/selectivity in a particular reaction. The analysis of steric environments around metal centers has traditionally dominated attempts to explain and predict the outcome of metal-based enantioselective processes. In comparison, the importance of electronic effects in asymmetric induction was appreciated only in recent years. Several catalytic systems known to date employ electronically diverse substituents on ligands in order to modulate reactivity of the metal center.[1] For example, in the catalytic asymmetric epoxidation of unfunctionalized olefins, electronic properties of substituents on chiral *salen* ligands determine the nature of transition state.[1a] The later transition state leads to higher enantioselectivities and electronic attenuation of electrophilic Mn=O centers affords higher levels of enantiomeric excess. Enhancement of enantioselectivity through incorporation of fluorine atoms on chiral phosphine ligands in the asymmetric hydrocyanation of olefins was documented.[1b] The concept of induced electronic asymmetry allows one to increase the enantioselectivity of rhodium-catalyzed hydroboration of olefins.[1c] Over the years, several modifications of the BINOL skeleton, aimed at changing its properties, have been reported.[3] For example, partially

hydrogenated BINOL was used as a catalyst precursor in enanatioselective alkylation of aldehydes,[3a] conjugate addition of diethylzinc to cyclic enones,[3b] and ring opening of epoxides.[3c] Incorporation of bromines into the 6 and 6' positions of BINOL, rather remote from the catalytic site, was shown to increase the enantioselectivity of the corresponding titanium catalysts in glyoxolate-ene reactions.[3d]

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for designing asymmetric catalysts derived from perfluoroarene ligands.

The present invention provides a new generation of asymmetric polyfluorinated catalysts. Fluorination of aromatic groups on a series of ligands drastically changes their properties including configurational stability and catalytic activity. The fundamental issue is the nature of steric and electronic effects of aromatic fluorination on binaphthol-based catalysts. The basic premise is that alteration of stabilizing stacking and edge-face interactions significantly affects approach of certain substrates to catalytic reaction centers. Due to the high electronegativity of fluorine, electron density in fluoronaphthyl rings is locoated at the periphery, rather than in the center. The present invention will be illustrated by examples such as preparation of enantiomerically pure fluorobinaphthol ligands and their application in catalytic asymmetric processes.

In one aspect of the invention there is provided method of producing asymmetric polyfluorinated catalysts, comprising: fluorinating aromatic groups on binaphthol-based catalysts.

In another aspect of the invention there is provided a method of producing a family of polyfluoroaryl ligand catalysts, comprising:

substituting at least one of the hydrogen atoms by fluorine (F) at any one of the 5,5',6,6',7,7',8,8' positions of 2,2'-dihydroxy-1,1'-binaphthyl (BINOL).

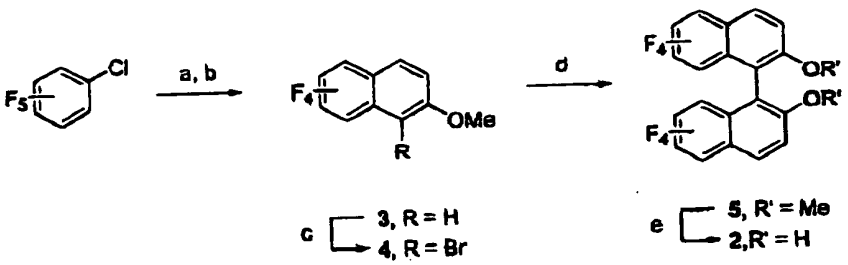
DETAILED DESCRIPTION OF THE INVENTION

The present invention will be exemplified, by way of example by disclosing the design a new family of polyfluoroaryl ligands that originate from 2,2'-dihydroxy-1,1'-binaphthyl (BINOL, 1), a catalyst precursor of broad utility in asymmetric catalysis.[2] Substitution of hydrogen atoms by fluorines at the 5, 5', 6, 6', 7, 7', 8, and 8' positions of BINOL has very small effect on the torsion angle but strongly affects distribution of electrons within the biaryl skeleton, which in turn greatly increases configurational stability of the corresponding enantiomers.

The inventors have reasoned that since the van der Waals radius of fluorine atom is about 0.27Å larger than that of hydrogen atom,[4] the replacement of hydrogens for fluorines at the 5, 5', 6, 6', 7, 7', 8, and 8' positions of BINOL may affect the torsion angle in the resulting 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (F_8BINOL, 2). More importantly, considerable electronic perturbations would take place due to the net effect of eight fluorine atoms. The electron-deficient nature of the aromatic rings in 2 should result in its higher oxidative stability compared to 1 and increased acidity of the hydroxyl groups which could potentially affect binding to metals and the corresponding substrates in the F_8BINOL-mediated reactions.

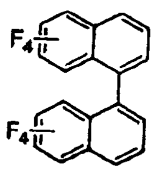
To prove these points, we prepared racemic form of **2** according to Scheme 1. Tetrafluorobenzyne, formed by treating commercially available chloropentafluorobenzene with *n*-butyllithium at -78°C, was reacted with 3-methoxythiophene, obtained from 3-bromothiophene using a literature procedure.[5] Upon the *in situ* extrusion of sulfur, 2-methoxy-5,6,7,8-tetrafluoronaphthalene **3** was obtained in x% yield. 5,6,7,8-Tetrafluoro-2-naphthol, prepared from **3** by demethylation with BBr_3, did not undergo the $FeCl_3$-catalyzed oxidative coupling, commonly used for the preparation of **1** from 2-naphthol.[6] Instead, substitution of hydrogen for chlorine at the 1 position of the aromatic ring took place. Higher oxidation potential of 5,6,7,8-tetrafluoro-2-naphthol (xV *vs* Ag/AgCl compared to xV *vs* Ag/AgCl for **1**) is a likely reason for the lack of reactivity in the oxidative coupling. We therefore reserved to the reductive route through intermediacy of the 1-brominated derivative **4**, prepared in 52% yield from **3** by treatment with *N*-bromosuccinimide in acetonitrile. The Ullmann homocoupling of **4**, facilitated by the presence of aromatic fluorines, gave the desired bis(methoxy) product **5** in x% yield. Demethylation of **5** with BBr_3 furnished F_8BINOL **2** in 88% yield. Finally, recrystallization from methanol/water gave pure **2** as white needles. After several unsuccessful attempts at resolving **2**, we were able to chromatographically separate the diastereomeric bis(menthyl)carbonates obtained by reacting racemic **2** with excess (-)-menthylchloroformate. Treatment of each diastereomer with dilute NaOH followed by extraction with diethyl ether afforded (-)-F_8BINOL and (+)-F_8BINOL, respectively. The enantiomeric excess, determined using chiral HPLC (Chiralpak AD column), was found to be >99.9% in each case.

Scheme 1[a]



[a]Key: (a) *n*-BuLi, ether, -78 °C; (b) 3-methoxythiophene, -78 °C to r.t.; (c) NBS, acetonitrile, r.t.; (d) Cu°, 175 °C; (e) BBr_3, dichloromethane, r.t.

Replacement of aromatic hydrogens for fluorines is known to substantially increase barriers to axial torsion in substituted biphenyls. For example, fluorination of the 4 and 5 positions of 9,10-dihydrophenanthrene raises the torsion barrier from 4.1 to 10.3 kcal/mol.[7] In order to estimate the effect of polyfluorination on atropisomerism in the octafluoro-1,1'-binaphthyl species we prepared racemic 5,6,7,8-octafluoro-1,1'-binaphthyl **6** and determined its X-ray structure.[8] We chose not to compare the torsion angles in the molecular structures of **1** and **2** due to the possibility of intramolecular OH-F hydrogen bonding in the crystal lattice that could have complicated direct comparison of geometric parameters. Remarkably, the torsion angle between the two tetrafluorinated naphthyl planes in **6** is only 0.7° larger than in the parent hydrido derivative (70.2° for octafluoro-1,1'-binaphthyl *vs* 69.5° for 1,1'-binaphthyl[9]). To further understand atropisomerism in **2** we investigated acid-promoted racemization of its (-) enantiomer. This process is known to operate for **1**. Remarkably, **2** remains optically active (99.9% e.e) after 24 hours in boiling THF/HCl mixture, whereas **1** rapidly racemizes under these conditions!



6

Polyfluorination of aromatic nuclei is also known to decrease pKa's of bound heteroatoms.[4] For example, incorporation of four fluorine atoms into the aromatic skeleton of tyrosine results in the pKa' decrease of the ring-bound hydroxyl group by 5 units.[10] We have found that the pKa' of the hydroxyl group in **2** decreases by 1 unit upon octafluorination (**1**: pKa' 10.28; **2**: pKa' 9.29). Another important consequence of fluorination is anodic shift in the oxidation potential of **2**, which was found to be more

positive than that of binaphthyl by xV, a useful property for applications in oxidation catalysis.

These results lead us to conclude that the effect of fluorine on the reactivity of F_8BINOL will be primarily electronic in nature. The desired conformational flexibility, one of the most important characteristics of BINOL allowing it to coordinate a wide variety of metals, should be preserved. Remarkable configurational stability of either enantiomer of 2 is perhaps its most valuable property. We are currently exploring the scope of the F_8BINOL-derived asymmetric catalysts. The method of the present invention may be used to produce a new Generation of Fluorobinaphthyl Catalysts for several applications including but not limited to: asymmetric catalysis with main group elements, transition metal and lanthanide metals; asymmetric reagent with main group elements, transition metal and lanthanide metals; polymer supported catalysis; nucleophilic displacement of fluorine atoms to modify characteristics of molecule (resulting compounds could be used same manner as original compound); incorporation of molecule into crown ethers for development of phase transfer catalysts; use of compound as a monomer for polymerization; asymmetric polymer supported electrochemical oxidation catalysis; as a chiral auxiliary in an asymmetric reaction; as a resolving agent for chiral compounds, including but not limited to amines; asymmetric catalysis (reagent) in fluorous phase reactions; as a chiral stationary phase for HPLC and other chromatographic techniques; phase transfer catalyst between organic, fluorous phase and alkali solutions.

The foregoing description of the preferred embodiments of the invention has been presented to illustrate the principles of the invention and not to limit the invention to the particular embodiment illustrated. It is intended that the scope of the invention be defined

by all of the embodiments encompassed within the following claims and their equivalents.

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THEREFORE WHAT IS CLAIMED IS:

1. A method of producing asymmetric polyfluorinated catalysts, comprising:

fluorinating aromatic groups on binaphthol-based catalysts.

2. A method of producing a family of polyfluoroaryl ligand catalysts, comprising:

substituting at least one of the hydrogen atoms by fluorine (F) at any one of the 5,5',6,6',7,7',8,8' positions of 2,2'-dihydroxy-1,1'-binaphthyl (BINOL).

3. A family of polyfluoroaryl ligands, comprising:

2,2'-dihydroxy-1,1'-binaphthyl (BINOL) with at least one of the hydrogen atoms substituted by fluorine (F) at any one of the 5,5',6,6',7,7',8,8' positions of the BINOL.

4. The use of the family of polyfluoroaryl ligands comprising 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) with at least one of the hydrogen atoms substituted by fluorine (F) at any one of the 5,5',6,6',7,7',8,8' positions of the BINOL as fluorobinaphthyl catalysts for an application selected from the group consisting of asymmetric catalysis with main group elements, transition metal and lanthanide metals, asymmetric reagent with main group elements, transition metal and lanthanide metals, polymer supported catalysis, nucleophilic displacement of

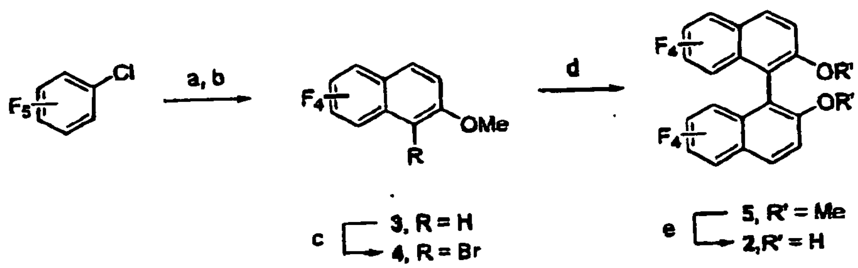
fluorine atoms to modify characteristics of molecule, incorporation of molecule into crown ethers for development of phase transfer catalysts, use of compound as a monomer for polymerization, asymmetric polymer supported electrochemical oxidation catalysis, as a chiral auxiliary in an asymmetric reaction, as a resolving agent for chiral compounds, including but not limited to amines, asymmetric catalysis (reagent) in fluorous phase reactions, as a chiral stationary phase for HPLC and other chromatographic techniques, and phase transfer catalyst between organic, fluorous phase and alkali solutions.

5. A molecule having the formula,

5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (F_8BINOL).

6. The molecule according to claim 5 produced according to scheme I

Scheme I



[a]Key: (a) *n*-BuLi, ether, -78 °C; (b) 3-methoxythiophene, -78 °C to r.t.; (c) NBS, acetonitrile, r.t.; (d) Cu°, 175 °C; (e) BBr_3, dichloromethane, r.t.

ABSTRACT

The present invention relates to the design and method of synthesis of asymmetric catalysts and more particularly the present invention provides a new generation of polyfluorinated catalysts. Fluorination of aromatic groups on a series of ligands drastically changes their properties including configurational stability and catalytic activity. The fundamental issue is the nature of steric and electronic effects of aromatic fluorination on binaphthol-based catalysts. The basic premise is that alteration of stabilizing stacking and edge-face interactions significantly affects approach of certain substrates to catalytic reaction centers. Due to the high electronegativity of fluorine, electron density in fluoronaphthyl rings is locoated at the periphery, rather than in the center.